Identifying and managing dermatologic toxicities associated with EGFR-inhibitor therapy

An educational resource for healthcare professionals
What to expect from EGFR-inhibitor therapy

The goal of EGFR-inhibitor therapy is to interrupt the growth and spread of tumor cells by disrupting the signals sent from the epidermal growth factor receptor (EGFR), which is found on the surface of some cancer cells. Because EGFR is also present on many normal cells in the body, including skin cells, dermatologic toxicity occurs in up to 90% of patients undergoing treatment. In its mild-to-moderate state, skin toxicity can cause physical pain and discomfort and take an emotional toll on patients. For some patients, side effects can be serious and potentially lead to life-threatening complications. In severe cases, the EGFR-inhibitor dose may be reduced, interrupted, or discontinued.

While there are currently no guidelines based on large, randomized clinical trials for the management of EGFR-inhibitor–related dermatologic toxicities, you play a key role in educating patients and families on treatment side effects, advising about appropriate interventions, and offering emotional support. Teaching patients how to recognize and manage treatment-related side effects, along with early intervention by healthcare professionals, is a necessary component of the overall treatment plan.
Time after initiation of EGFR-inhibitor therapy to appearance of selected dermatologic toxicities

Clinical transformation of rash\textsuperscript{5}

Rash associated with EGFR-inhibitor therapy generally develops and evolves over the first 2 weeks of treatment. Patients typically experience a sensory facial disturbance with edema soon after initiation of therapy. This is followed by a papulopustular eruption localized to the face and upper trunk. Left untreated, the rash may then exhibit crusting, which may develop into small, dilated blood vessels near the surface of the skin (telangiectasias). A typical course for rash development is over a 4-week period.
Rash: Acne/Acneiform

- Occurs in 53% to 100% of patients\textsuperscript{6}
- Usually develops within the first 2 weeks of starting therapy\textsuperscript{4,7}
- May spontaneously improve or resolve with continued use of EGFR-inhibitor therapy\textsuperscript{7}
- Frequent localization to the face, neck, and upper trunk\textsuperscript{7}
- Associated with pruritus and tenderness\textsuperscript{7}
Xerosis (dry skin)

- Occurs in 4% to 35% of patients\(^1\)
- Develops after 1 to 2 months of therapy\(^4\)
- Appears over the extremities, scalp, and areas associated with papulopustular rash\(^6\)
- May result in chronic asteatotic eczema\(^6\)
- May be complicated by bacterial and viral superinfection\(^6\)

Photosensitivity/Erythema

- Photosensitization occurs commonly with EGFR-inhibitor therapy\(^{3,8}\)

All images above: Data on file, Amgen.
Suggestions for patients

General recommendations

• Avoid sun exposure and use sunscreen with SPF $\geq 30^8$
• Avoid over-the-counter acne medications, creams, and gels$^3$
• Use mild soaps and shampoos$^8$
• Use moisturizing creams and ointments$^3$
• Use hypoallergenic makeup, if desired$^2$

For specific dermatologic toxicities$^2$

• Dry skin
  - Moisturizing creams and lotions
  - Nondetergent, neutral pH products
• Itching
  - Topical analgesics
  - Concentrated lotions
  - Zinc-oxide–based calamine lotion
  - Hydrocortisone cream
• Dryness or flaking on palms/soles
  - Exfoliating scrub
  - Moisturizing creams and lotions

Notes:

For dry skin:

______________________________
______________________________
______________________________

For itching:

______________________________
______________________________

For dryness or flaking on palms/soles:

______________________________
______________________________
Nail changes

- Occur in 2% to 30% (all grades) of patients on EGFR inhibitors\(^1,3,6,8\)
- Usually develop 1 to 4 months after therapy\(^5-7\)
- Can be associated with tenderness\(^1,6,7\)
- May mimic ingrown toenail\(^6,9\)
- Superinfection may occur—cultures should be obtained when discharge is present\(^6,9\)

Suggestions for patients

General recommendations

• Avoid pushing back your cuticles or biting your nails\textsuperscript{8,10}
• Do not use acrylic nails\textsuperscript{8}
• Use emollients with topical petroleum around nails\textsuperscript{10}
• Wear rubber or cotton-lined gloves when washing dishes or cleaning\textsuperscript{8,10}

Products to recommend to your patients\textsuperscript{5,6}

• Topical antibiotic creams

Notes:
Other dermatologic toxicities\textsuperscript{11}

- Hair disorders
  - Alopecia of scalp and beard
  - Increased hair growth on the face (hirsutism) and eyelashes (hypertrichosis)

- Fissures

Secondary skin infections

Secondary skin infections
- Secondary infections are characterized by:
  - Yellowish brown crust overlaying inflammatory lesions
  - Significant oozing or fluid from lesions
  - An abrupt change in the appearance of lesions
    (particularly if lesions differ from those in other areas)

Preventing secondary infections
- Consider intranasal mupirocin treatment
- Short course of oral antibiotics

Treatment
- Culture pustule and treat accordingly
NCI-CTCAE Grading Guidelines

The NCI-CTCAE is a descriptive terminology used for adverse event reporting.

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash acneiform</strong></td>
<td>Papules and/or pustules covering &lt; 10% of body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10%-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL)</td>
<td>Papules and/or pustules covering &gt; 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
</tr>
<tr>
<td><strong>Dry skin</strong></td>
<td>Covering &lt; 10% BSA and no associated erythema or pruritus</td>
<td>Covering 10%-30% BSA and associated with erythema or pruritus; limiting instrumental ADL</td>
<td>Covering &gt; 30% BSA and associated with pruritus; limiting self care ADL</td>
<td>–</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>Mild or localized; topical intervention indicated</td>
<td>Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</td>
<td>Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</td>
<td>–</td>
</tr>
</tbody>
</table>

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# NCI-CTCAE Grading Guidelines

Continued from previous page

<table>
<thead>
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<th></th>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Photo-sensitivity</strong></td>
<td>Painless erythema and erythema covering &lt; 10% BSA</td>
<td>Tender erythema covering 10%-30% BSA</td>
<td>Erythema covering &gt; 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (eg, narcotics or NSAIDs)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td><strong>Paronychia</strong></td>
<td>Nail fold edema or erythema; disruption of the cuticle</td>
<td>Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL</td>
<td>Surgical intervention or IV antibiotics indicated; limiting self care ADL</td>
<td>–</td>
</tr>
</tbody>
</table>

For more detailed information, please refer to the NCI-CTCAE Grading Guidelines.
Treatment algorithms for managing rash and nail changes

Currently, there is no standard approach to the management of dermatologic side effects associated with EGFR-inhibitor treatment. Treatment algorithms in this section are compiled from a review of literature of common approaches to skin reactions. Individual clinical judgment must be applied when reviewing the following recommendations.
## Treatment algorithm: Management of cutaneous conditions

Individual clinical judgment must be applied when reviewing the following recommendations.

### Rash severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
</table>
| • Generally localized  
• Minimally symptomatic  
• No impact on ADL  
• No sign of additional infection | • Generalized  
• Mild symptoms (eg, pruritus, tenderness)  
• Minimal impact on ADL  
• No sign of additional infection | • Generalized  
• Severe symptoms (eg, pruritus, tenderness)  
• Significant impact on ADL  
• Potential for additional infection |

### Intervention

#### Mild
- Continue EGFR inhibitor at current dose and monitor for change in severity
- No treatment or Topical hydrocortisone 1% or 2.5% cream* and/or clindamycin 1% gel
  - Reassess after 2 weeks (either by healthcare professional or patient self report); if reactions worsen or do not improve, proceed to next step

#### Moderate
- Continue EGFR inhibitor at current dose and monitor for change in severity—continue treatment of skin reaction with the following:
  - Hydrocortisone 2.5% cream* or clindamycin 1% gel or pimecrolimus 1% cream
  - PLUS doxycycline or minocycline
  - Reassess after 2 weeks (either by healthcare professional or patient self report); if reactions worsen or do not improve, proceed to next step

#### Severe
- Reduce EGFR-inhibitor dose as per label and monitor for change in severity—continue treatment of skin reaction with the following:
  - Hydrocortisone 2.5% cream* or clindamycin 1% gel or pimecrolimus 1% cream
  - PLUS doxycycline or minocycline
  - PLUS methylprednisolone
  - Reassess after 2 weeks; if reactions worsen, EGFR-inhibitor dose interruption or discontinuation may be necessary

*The use of topical steroids should be employed in a pulse manner based on your institution’s guidelines.

Treatment algorithm: **Management of cutaneous conditions**\(^1\)\(^3\)

Individual clinical judgment must be applied when reviewing the following recommendations.

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Macular rash</th>
<th>Pustular rash</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Hydrocortisone</strong> topical cream/lotion</td>
<td><strong>Clindamycin</strong> gel for isolated scattered lesions; <strong>clindamycin</strong> lotion for multiple scattered areas</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>If &gt; 2 body regions, consider oral <strong>methylprednisolone</strong>; <strong>fluticasone</strong> topical steroid if limited to &lt; 2 body regions</td>
<td>Oral antibiotics: <strong>Minocycline</strong> or <strong>trimethoprim/sulfamethoxazole</strong></td>
<td>Topical antihistamine or oral <strong>diphenhydramine</strong> or <strong>hydroxyzine</strong></td>
</tr>
<tr>
<td>3</td>
<td>Oral <strong>methylprednisolone</strong></td>
<td>Oral antibiotics: <strong>Minocycline</strong> or <strong>trimethoprim/sulfamethoxazole</strong></td>
<td>Oral <strong>diphenhydramine</strong> or <strong>hydroxyzine</strong></td>
</tr>
</tbody>
</table>
Treatment algorithm: **Management of xerosis**

Individual clinical judgment must be applied when reviewing the following recommendations.

### Grade 1
- **Emollients**

### Grade 2/3
- Ammonium lactate 12% and/or urea 40% to palms and soles
  - 2-week reassessment

### Xerotic dermatitis
- Combination topical steroids + urea 20%
  - 2-week reassessment

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Treatment algorithm: **Management of pruritus**

### Grade 1
- Topical preparations pramoxine/lidocaine

### Grade 2/3
- Oral antihistamines
  - 2-week reassessment
Treatment algorithm: **Management of nail toxicities**

Individual clinical judgment must be applied when reviewing the following recommendations.

<table>
<thead>
<tr>
<th>Prophylaxis/Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3 (Refractory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonium lactate 12% or urea 40% + Vinegar soaks using a 1:10 dilution in water*</td>
<td>Topical† or intralesional corticosteroids</td>
<td>Culture/sensitivities + Systemic antibiotics</td>
<td>Culture/sensitivities + Systemic antibiotics + Nail avulsion</td>
</tr>
<tr>
<td><strong>2-week reassessment</strong></td>
<td><strong>2-week reassessment</strong></td>
<td><strong>2-week reassessment</strong></td>
<td><strong>2-week reassessment</strong></td>
</tr>
</tbody>
</table>

* Soaking fingertips in 1:10 white vinegar in water for 5 minutes a day.
† Such as clobetasol ointment or flurandrenolide (Cordran®) adhesive tape.

Summary

- Teaching patients how to recognize and manage rash and nail changes, along with early intervention, is necessary.\(^3\)
- It’s always important to advise patients that if they do experience rash or other skin toxicity, they should consult with a healthcare professional right away.
- Patients should also know:
  - Dermatologic toxicities are a class effect of EGFR inhibitors.\(^1\)
  - Skin toxicity is usually mild to moderate in nature, but in some cases may progress and become life threatening.\(^2\)
  - Skin effects typically appear within 2 weeks of starting therapy and may transform as treatment continues.\(^4\)
  - The most common toxicities include papulopustular rash, dry skin, pruritus, photosensitivity, and nail changes.\(^1\)
- Currently, the only available guidelines for clinical management of EGFR-inhibitor-mediated dermatologic toxicities are based on expert opinions and clinical experience, but are not evidence-based.\(^1\)

Refer patients to a dermatologist when:\(^2\):
- Lesions with an uncharacteristic appearance or distribution are present.
- Necrosis, blistering, or petechial/purpurial lesions occur.
- Patients manifest atypical dermatologic manifestations unrelated to rash.
Contact your Amgen representatives to request more information or materials. If you have any other questions, you may contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436).